Mineralocorticoid Signaling in Transition to Heart Failure With Normal Ejection Fraction

Brian P. Shapiro, Theophilus E. Owan, Selma Mohammed, Martina Kruger, Wolfgang A. Linke, John C. Burnett, Jr, Margaret M. Redfield

Abstract—Heart failure with normal ejection fraction occurs in elderly patients with hypertensive heart disease. We hypothesized that, in such patients, mineralocorticoid receptor activation accelerates the types of ventricular and vascular remodeling and dysfunction believed important in the transition to heart failure. We tested this hypothesis by administering deoxycorticosterone acetate (DOCA) without salt loading or nephrectomy to elderly dogs with experimental hypertension. Elderly dogs were made hypertensive by renal wrapping. After 5 weeks, dogs were randomly assigned to DOCA (1 mg/kg per day IM; old hypertensive [OH] + DOCA; n = 11) or not (OH; n = 11) for 3 weeks. At week 8, conscious echocardiography and hemodynamic assessment under anesthesia were performed. DOCA resulted in further increases in conscious blood pressure (P<0.05) without increases in cardiac output or diastolic volume. In the conscious state, effective arterial elastance (P<0.05) and systemic vascular resistance (P=0.06) were increased, and systemic arterial compliance (P<0.05) was decreased in OH+DOCA animals. After anesthesia, instrumentation, and autonomic blockade, blood pressure was lower, whereas left ventricular (LV) systolic elastance, LV diastolic stiffness, and ex vivo myofiber diastolic stiffness were increased in OH+DOCA animals. LV collagen was increased in OH+DOCA animals (P<0.05 for all), but LV mass, LV brain natriuretic peptide, and titin isoform profiles were not. Neither aortic stiffness nor aortic structure was altered in OH+DOCA animals. These findings suggest that age and hypertensive heart disease enhance sensitivity to exogenous mineralocorticoid administration and that mineralocorticoid receptor activation could contribute to the transition to heart failure in elderly persons by promoting increases in LV diastolic and systolic stiffness. (Hypertension. 2008;51:289-295.)

Key Words: heart failure ■ hypertension ■ collagen ■ diastole

Heart failure (HF) with normal ejection fraction (HFnlEF) comprises nearly half of the cases of HF and poses a substantial public health problem.1 Advanced age and systemic hypertension are the dominant risk factors for HFnlEF. The presence of neurohumoral activation in HFnlEF and its role in mediating the transition from hypertensive heart disease (HHD) to HFnlEF has not been well studied. Mineralocorticoid (MC) receptor (MR) antagonism has been repeatedly demonstrated to reduce cardiac hypertrophy and fibrosis in experimental and human hypertension.2,3 However, in young normal animals, the hypertensive and cardiac remodeling effects of experimental MC excess are dependent on concomitant salt loading (and unilateral nephrectomy).2,4 The mechanisms whereby salt loading exacerbates the effects of exogenous MC administration on the heart and vasculature are unclear, and other factors present in HHD,5 vascular disease,6 or HF7 may also sensitize the cardiovascular system to the adverse effects of exogenous MC excess. Indeed, a recent study showed that aldosterone levels correlate potently with mortality in HF regardless of the level of systolic function.8 We hypothesized that, in the presence of advanced age and pre-existing HHD, exogenous MC excess (in the absence of salt loading or nephrectomy) accelerates the types of ventricular and vascular remodeling and dysfunction believed important in the transition of HHD to HFnlEF. We tested this hypothesis by administering an MR agonist (deoxycorticosterone acetate [DOCA]) without an enhanced sodium diet to elderly dogs with experimental hypertension and stable HHD and assessed its effect on ventricular and vascular structure and function.

Methods

This study was approved by the Mayo Institutional Animal Care and Use Committee, and euthanasia was performed in accordance with guidelines set forth by the panel on euthanasia of the American Veterinary Medical Association. Please see http://hyper.ahajournals.org for supplemental material detailing the description of methods.
Experimental Design
Old mongrel dogs (n=22; age 8 to 12 years) underwent bilateral renal wrapping to induce chronic hypertension (old hypertensive [OH]), as described previously.9 A central aortic catheter was inserted for weekly measurement of blood pressure (BP). Hypertension was allowed to fully develop over 5 weeks. Then, dogs were randomly assigned to receive DOCA (1 mg/kg IM once daily) for the final 3 weeks (OH+DOCA; n=11) or continued observation (OH; n=11). At the end of week 8, dogs underwent conscious echocardiography, acute hemodynamic study, and tissue harvest. All of the dogs were fed standard dry dog chow containing 0.42% sodium.

Conscious Studies
Two-dimensional guided M-mode echocardiography along with BP measurement was performed to assess left ventricular (LV) end-diastolic and LV end-systolic volumes (Teichholz formula), stroke volume, cardiac output, and ejection fraction. Effective arterial elastance (0.9*systolic BP/stroke volume), systemic vascular resistance (mean BP/CO), and systemic arterial compliance (stroke volume/pulse pressure) were calculated.

Acute Hemodynamic Study
Dogs were anesthetized with fentanyl (0.25 mg/kg bolus followed by 0.18 mg/kg per hour) and midazolam (0.75 mg/kg bolus followed by 0.59 mg/kg per hour), given autonomic blockade, and instrumented with LV and aortic micromanometer catheters, piezoelectric crystals for LV volume, an aortic flow probe, an atrial pacemaker, and a caval occluder. Data were collected at baseline (BL), after volume expansion (VE) with dextran (250 mL over 15 minutes), and during phenylephrine infusion (PE) to increase peripheral resistance.

Acute IVC occlusion was used to define the end-systolic pressure (ESP) volume relationship [ESP=Eo*(ESP volume-Vo)], and the end-diastolic pressure volume relationship [end-diastolic pressure=α*(Edv+β)] where β represents the diastolic stiffness coefficient and α, the curve fitting constant. To account for nonlinear covariance of α and β, end-diastolic volume (EDV) at a common end-diastolic pressure of 20 mm Hg was calculated (EDV20=ln20/α/β), where a lower EDV20 reflects increased diastolic stiffness.10–12

Effective arterial elastance (Ea) and systemic vascular resistance (SVR) were calculated from invasive data. The aortic stiffness index (βaortic) is independent of distending pressure and is calculated as βaortic=[Dd ln (Ps/Pd)]/[Ds−Dd] where Dd and Ds are the diastolic and systolic aortic diameter and Ps and Pd are aortic systolic and diastolic pressure, respectively.13 The characteristic aortic impedance (Za) was calculated from the mean of impedance moduli from 2 to 5 Hz.14 Systemic arterial compliance (SAC) was calculated by the method of Liu et al.14

Neurohumoral Analysis
Blood samples were collected before renal wrap and at week 8. Procollagen III, angiotensin II, aldosterone, creatinine, brain natriuretic peptide, and transforming growth factor-β1 content were measured in plasma or tissue.

Histological Analysis
Tissue was stained with picrosirius red to assess collagen volume fraction and aortic Verhoeven’s Van Gieson stain for elastin density by quantitative histomorphometry (Zeiss Vision). Aortic wall thickness was averaged from 5 measurements.

Total Collagen Content and Cross-Linking
Total collagen and collagen solubility were measured by the hydroxyproline assay in the left ventricle and aorta.

Titin Isoform Composition and Myofiber Stiffness
The abundance of the more compliant N2BA isoform as a percentage of total titin was measured by gel electrophoresis.15 Passive tension from isolated, skinned myofiber bundles from 3 dogs in each group

Figure 1. Conscious BP measurements. Systolic BP was elevated at 1 week postrebral wrapping with progressive increases in diastolic BP over 5 weeks. In OH dogs, BP remained stable over weeks 6 to 8, whereas both systolic and diastolic BPs increased significantly in OH+DOCA dogs during the 3-week DOCA administration.

was also determined, where the means of 3 to 5 individual fiber measurements from each dog were averaged.15

Statistics
Data are expressed as mean±SD. Continuous variables were compared by a paired or unpaired (as appropriate), 2-sided Student’s t test with an α of 0.05. Data with a skewed distribution were subjected to log transformation before analysis. Multiple linear regression was used to model the relationship between parameters and multiple covariables. The relationship between tension (normalized to fiber area) and sarcomere length was modeled as a polynomial regression and differences between groups compared by ANOVA as described previously.15

Results
Conscious Assessment
Systolic and diastolic BPs were similarly elevated in both groups before the initiation of DOCA (Figure 1). Systolic and diastolic BPs increased during the 3 weeks of DOCA treatment in OH+DOCA animals but remained stable over this time period in the OH dogs. Pulse pressure was similar between groups. Effective arterial elastance and SVR tended to be higher, whereas systemic arterial compliance was lower in OH+DOCA animals (Figure 2A through 2C). The cardiac output, LV end-diastolic volume, and ejection fraction were similar between groups (Figure 2D through 2F).

Biomarkers
During the 8 weeks, the rise in brain natriuretic peptide concentration and procollagen III, a marker of collagen synthesis, was greater in OH+DOCA dogs than in OH dogs (Table 1). Angiotensin II fell sharply in OH+DOCA dogs, consistent with DOCA’s negative feedback on angiotensin II production. Aldosterone levels were undetectable (<2.5 pg/mL) in all but 3 of the dogs before wrapping and in all but 2 of the dogs at 8 weeks after wrapping. Creatinine was unchanged from BL in both groups.

Anesthetized Study
LV Systolic Function
Although OH+DOCA animals had higher BP and similar EDV during conscious studies, after anesthesia, surgical instrumentation, and autonomic blockade, LV systolic pressure and EDV were lower at BL, during VE and PE, and overall (Figure 3A and 3B). End-systolic elastance (Ees) was
Increased in OH+DOCA dogs at BL, during VE and PE infusion, and overall (Figure 3C).

LV Diastolic Function
The diastolic stiffness coefficient (β) was increased in OH+DOCA dogs at BL and overall (Figure 4A). During VE and PE infusion, there were concomitant and variable changes in β and the curve-fitting constant α (Figure 4B). Over all of the experimental periods, α and β were inversely and nonlinearly related (Figure 4C), and EDV20, which accounts for this covariance, was lower in OH+DOCA animals at all of the time periods, reflecting the upward and leftward shifts of the end-diastolic pressure volume relation in OH+DOCA dogs (Figure 4D). Consistent with in vivo measurements, myofibers isolated from OH+DOCA dogs displayed increased passive stiffness as compared with those isolated from OH dogs (Figure 5A). Consistent with the concept of time-varying elastance, LV diastolic stiffness increased (lower EDV20) with increases in LV systolic stiffness (r=-0.82; P<0.0001), but EDV20 was lower (greater diastolic stiffness) in OH+DOCA animals (P=0.008) when adjusting for systolic stiffness (P<0.0001; model r²=0.79).

Table 1. Biomarkers Before and 8 Weeks After Renal Wrapping

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Baseline</th>
<th>Week 8</th>
<th>Baseline</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen III, pg/mL</td>
<td>19.3±6.3</td>
<td>19.3±5.2</td>
<td>13.4±3.7</td>
<td>20.1±4.0*</td>
</tr>
<tr>
<td>Log angiotensin II, pg/mL</td>
<td>0.38±0.41</td>
<td>0.63±0.67</td>
<td>0.67±0.40</td>
<td>0.19±0.30*</td>
</tr>
<tr>
<td>Log BNP, pg/mL</td>
<td>0.83±0.18</td>
<td>1.0±0.35</td>
<td>0.74±0.09</td>
<td>1.2±0.38†</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.75±0.20</td>
<td>0.80±0.24</td>
<td>0.69±0.15</td>
<td>0.76±0.18</td>
</tr>
</tbody>
</table>

*P<0.05 vs baseline.
†P<0.05 vs OH.

LV Structure
LV hypertrophy as assessed by LV mass/body weight and LV brain natriuretic peptide concentrations was similar between groups (Table 2). Total LV collagen, quantified by histomorphometry and absorbance spectroscopy, was increased in OH+DOCA dogs, but LV collagen solubility was similar between groups. The correlation between diastolic stiffness measures and LV collagen content was not strong (r=0.45; P=0.045 for collagen volume fraction versus EDV20). There was no difference in the LV transforming growth factor-β1 concentration on ELISA or Western blot assays. The relative abundance of the more compliant N2BA titin isoform was also similar between the groups (Figure 5B and 5C).

Vascular Function
Because vascular properties vary with distending pressure, they were assessed over the range of conditions present at BL and with VE and PE infusion. Overall, mean arterial pressure and SV were lower in OH+DOCA dogs (Figure 6A and 6B), whereas heart rate (Figure 6C) was similar. Thus, Ea and SVR were similar in the 2 groups (Figure 6D and 6E). Diastolic and systolic aortic dimensions increased with distending (mean arterial) pressure (P<0.0001) and, after adjusting for distending pressure and body size, were similar between groups (P=0.35). Both Zo and the aortic stiffness coefficient β were similar between groups (Figure 6F and 6G). In contrast to conditions observed in the conscious state, SAC was increased in OH+DOCA animals after autonomic blockade (Figure 6H). Overall, systemic arterial compliance was inversely related to SVR (r=−0.67; P<0.0001).

Ventricular-Arterial Coupling
The systolic ventricular-arterial coupling ratio (Ees/Ea) was increased in OH+DOCA versus OH dogs (1.6±1.9 versus 0.7±0.3; P=0.01), reflecting the chronic increases in LV elastance and the reduced arterial load in the anesthetized,
autonomic blocked state. The LV ESP measured during the steady-state recordings was related (model $r^2=0.86$; $P<0.0001$) to preload (EDV; $P<0.0001$), contractility assessed at each corresponding experimental period (log Ees; $P<0.0001$) and $V_o$ ($P<0.0001$), and vascular properties (SVR $[P<0.0001]$, characteristic aortic impedance $[P=0.045]$, and SAC $[P=0.047]$). There was no difference in ESP between groups when adjusting for the ventricular and vascular properties ($P=0.49$).

**Aortic Structure**

Ex vivo aortic wall thickness was similar between groups (Table 2). There was no difference in aortic elastin density, total collagen content (by quantitative histomorphometry or hydroxyproline assay), or collagen solubility in OH+DOCA versus OH dogs.

**Discussion**

In these elderly canines with pre-existing age- and hypertension-related vascular and ventricular remodeling and dysfunction, DOCA increased BP without salt loading or nephrectomy. Neither aortic structure nor load-independent vascular stiffness measures were further altered in OH+DOCA animals, suggesting that the DOCA-induced worsening of hypertension was mediated by increases in resistance and reduction in SAC. In contrast, both systolic and diastolic LV stiffness and passive LV myofiber stiffness were increased in association with increased LV fibrosis but not increased hypertrophy or titin isoform changes. The OH+DOCA dogs were more sensitive to autonomic blockade and the preload reducing effect of anesthesia with a more profound reduction in BP.

Age-associated changes in cardiac and vascular structure and function alter the substrate on which cardiovascular disease is superimposed and modify the threshold at which a specific perturbation may produce biologically or clinically important manifestations. Thus, we sought to examine the impact of experimental MC excess on cardiovascular structure and function against the background of advanced age and HHD and without increases in dietary sodium intake. Aldosterone is a sodium-retaining and potassium- and magnesium-wasting hormone that modulates electrolyte homeostasis in epithelial cells. Levels of aldosterone (relative to renin) increase with age, are higher in women, and are associated with BP and the incidence of hypertension. Aldosterone levels are associated with poor outcomes in HF. However, its cardiac and vascular effects are complex and somewhat
Aortic pathology

Table 2. LV and Aortic Pathology

<table>
<thead>
<tr>
<th>Variable</th>
<th>OH</th>
<th>OH+DOCA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV pathology</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LV mass/body weight, mg/kg</td>
<td>5.6±0.3</td>
<td>5.8±0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Log LV BNP, pg/mg of protein</td>
<td>4.0±4.6</td>
<td>5.7±5.5</td>
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</tr>
<tr>
<td>Total collagen, μg/mg of tissue weight</td>
<td>2.6±0.5</td>
<td>3.1±0.6</td>
<td>0.0005</td>
</tr>
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<td>Collagen volume fraction, %</td>
<td>4.1±2.0</td>
<td>7.2±2.0</td>
<td>0.043</td>
</tr>
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<td>Insoluble collagen, %</td>
<td>52.4±2.9</td>
<td>52.7±6.5</td>
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<tr>
<td>TGF-β1, ELISA, pg/mg of protein</td>
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<tr>
<td>TGF-β1, Western blot, %</td>
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Aortic pathology

- Aortic wall thickness, μm: 1695±318 vs 1588±240, P = 0.4
- Elastin volume fraction, %: 42.5±7.8 vs 45.8±10.2, P = 0.4
- Total collagen, μg/mg of tissue weight: 68.2±19.3 vs 64.1±17.0, P = 0.6
- Collagen volume fraction, %: 23.3±4.7 vs 26.7±7.4, P = 0.2
- Insoluble collagen, %: 11.4±6.5 vs 15.7±5.3, P = 0.09

TGF-β1 indicates transforming growth factor-β1; BNP, brain natriuretic peptide.

controversial. Complexity stems from the realization that aldosterone, like other steroids, possesses rapid, “nongenomic” effects, some of which may be not mediated by MR. Further complexity stems from the interaction of aldosterone, glucocorticoids, and the MR in cells where 11β-hydroxysteroid dehydrogenase type 2 is present (renal tubule). The course of cardiovascular remodeling and dysfunction associated with elevated MC inappropriate for salt intake is accelerated by uninephrectomy, and the unique renal injury associated with renal wrapping may serve a similar permissive role here. We speculate that renal dysfunction may uniquely contribute to the substrate needed for MR activation. Renal dysfunction is potently associated with progression of cardiovascular disease to HF, and sensitization of the cardiovascular system to the effects of MC or MR activation without MC excess may contribute to this well-recognized cardiorenal interaction in HHD and HF. Of note, we did not find evidence of increased transforming growth factor-β in the hearts of OH+DOCA dogs, although this mediator of fibrosis was only measured at 1 time point.

In young normal animals, experimental MC administration does not result in hypertension or cardiac remodeling unless administered in the presence of salt loading (and unilateral nephrectomy). The mechanisms mediating the salt-MC-renal dysfunction interaction observed in the DOCA-salt model are not entirely clear. Funder and others have convincingly argued that the effects of experimental MC excess may be mediated by a proinflammatory effect of MC salt and associated increases in oxidative stress, which activate glucocorticoid-bound vascular or cardiac MR through redox changes, rather than by a direct effect of MC binding to the MR. Furthermore, oxidative stress may result in MR activation even in the absence of exogenous MC administration. Weber and colleagues have provided extensive evidence that MC excess and activation of epithelial cell MR leads to loss of divalent cations (Ca²⁺ and Mg²⁺), secondary hyperparathyroidism, and parathyroid hormone–mediated intracellular Ca²⁺ loading, a potent mediator of oxidative stress. This paradigm may also provide insight into the interaction between salt loading and MC effects, because increased sodium intake exacerbates Ca²⁺ losses in the distal tubule. The course of cardiovascular remodeling and dysfunction associated with elevated MC inappropriate for salt intake is accelerated by uninephrectomy, and the unique renal injury associated with renal wrapping may serve a similar permissive role here. We speculate that renal dysfunction may uniquely contribute to the substrate needed for MR activation. Renal dysfunction is potently associated with progression of cardiovascular disease to HF, and sensitization of the cardiovascular system to the effects of MC or MR activation without MC excess may contribute to this well-recognized cardiorenal interaction in HHD and HF. Of note, we did not find evidence of increased transforming growth factor-β in the hearts of OH+DOCA dogs, although this mediator of fibrosis was only measured at 1 time point.

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TGF-β1 indicates transforming growth factor-β1; BNP, brain natriuretic peptide.

Figure 6. Invasive assessment of vascular function. After anesthesia, instrumentation, and autonomic blockade, the LV ESP, mean arterial pressure (MAP; A), and stroke volume (SV; B) were lower in the OH+DOCA dogs. Heart rate (HR; C), Ea (D), characteristic aortic impedance (Zc; E), and aortic stiffness index (β_aorta; F) were similar between groups. SAC (F) was higher in OH+DOCA dogs.
and serial assessment may have provided more insight into the signaling associated with DOCA effects.26,27

The vascular effects of MC in this model deserve comment. After 3 weeks of DOCA, there was increased vascular tone in the conscious state. The enhanced sensitivity to autonomic blockade and the preload-reducing effects of anesthesia observed during the anesthetized state may reflect the baroreceptor desensitization described previously with DOCA,28 as well as the increased LV systolic and diastolic stiffness, both of which enhance sensitivity to volume changes.29,30 such as can occur with anesthesia and surgical instrumentation. Increases in aortic fibrosis or stiffness were not observed. Jones and colleagues31,32 described very early alterations in vascular smooth muscle ion flux, aortic smooth muscle cell hypertrophy, and enhanced sensitivity to circulating vasoconstrictors, which may contribute to altered vascular function with MC excess independent from any alterations in aortic collagen. Lacolley et al33 found that, in elderly normotensive rats, MR antagonists did not alter aortic structure but did modestly effect carotid fibrosis. Smaller arteries, which contain more vascular smooth muscle, may be more sensitive to the effects of MC. Sun et al34 reported that the increases in vascular collagen with MC excess are predominately adventitial (perivascular). However, we could not assess perivascular fibrosis in coronary arteries as is possible in rodents with prominent intramyocardial coronary arteries. In this elderly hypertensive model, there is elastin degradation, increased collagen, and decreased collagen solubility in the aorta,10 and these pre-existing age- and hypertension-related changes may modify the large artery response to MC excess.

The finding of increased LV diastolic and passive LV myofiber stiffness may be related to the observed increases in the extracellular matrix. The techniques used to isolate myofibers do not remove collagen fibers, and, thus, the observed changes in passive myofiber stiffness cannot discriminate between changes in intrinsic myocyte stiffness versus extracellular matrix changes. However, titin isoform composition remained unaltered in DOCA-administered OH hearts, and because myofibrillar passive stiffness depends on titin isoform expression,35 it is unlikely that alterations in sarcomeric passive stiffness account for the increased passive myofiber stiffness. Whether other cytoskeletal structures contribute to the DOCA-induced stiffening could be interesting to test in future studies on isolated myocytes, because the degree of myocardial fibrosis associated with DOCA administration, although highly significant, was not dramatic (≈25% by the hydroxyproline assay and ≈75% by histomorphometry). The relatively weak correlation between fibrosis and diastolic stiffness measures may suggest that intrinsic cardiomyocyte changes36 contribute to the observed changes in LV diastolic function.

The increased systolic stiffness in OH+DOCA dogs reflects chronic coupling of LV systolic function to the enhanced arterial load associated with DOCA administration. Of note, this enhanced systolic performance occurred in the absence of detectable increases in LV mass or LV brain natriuretic peptide concentrations (a reliable measure of cardiomyocyte hypertrophy), as has been observed in humans.30,37 Although the acute effects of anesthetics and autonomic blockade reduced arterial load, the increases in Ees were still apparent, and, thus, under these experimental conditions, there was an increase in the coupling ratio (Ees/Ea), which would likely not have been observed in the conscious, nonblocked state. Although chronic coupling of systolic stiffness to arterial load preserves stroke work, increases in systolic and diastolic stiffness increase sensitivity to changes in volume and limit systolic reserve, effects that may contribute to BP lability and exercise intolerance common in HFnIEF.29,38

Limitations
No assessment of sodium balance was performed, but the conscious hemodynamics do not suggest ongoing volume overload. Load-independent assessment of LV and vascular function in the conscious state would have been preferable. We did not assess MR density. However, neither cardiac-specific or systemic overexpression of MR in mouse models leads to changes similar to those observed here.39,40

Perspectives
The emerging role of MR antagonism in the treatment of HF and HHD has renewed interest in understanding the role of MC and the MR in the pathophysiology of HF. The current data suggest that MR activation may promote increased systolic and diastolic stiffness and, thus, the transition from HHD to HFnIEF in elderly persons. Whether therapy with MR antagonists can improve outcomes in HFnIEF is currently being tested in a large clinical trial (Trial of Aldosterone Antagonist Therapy in Adults With Preserved Ejection Fraction Congestive Heart Failure, www.clinicaltrials.gov). Further studies are needed to clarify whether and how MR activation occurs in HHD and HFnIEF and the mechanisms underlying the unique cardiorenal-MC interaction in HHD.

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Disclosures
None.

References


41. Shapiro et al. Aldosterone and HFnlEF
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